REMARKS

Claims 1-10 and 20 are pending in this application. Claims 11-19 and 21 were previously withdrawn.

I. CLAIM REJECTIONS ON THE GROUND OF NONSTATUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING

The Examiner has provisionally rejected Claims 1, 3 and 20 as not patentably distinct from Claims 19-22 of U.S. Patent Application Serial No. 11/488,693 and has rejected Claims 1-6 and 20 as not patentably distinct from Claims 1-3, 5 and 7-12 of United States Patent No. 7,084,105 in view of Yamada et al. Office Action at 3. Applicants respectfully traverse.

Applicants maintain their position that Examiner's rejections should be held in abeyance pending the allowance of claims. The Examiner has instructed that a terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting ground. Without acquiescing to the propriety of the Examiner's rejections, and specifically the Examiner's interpretation of what the cited references teach or claim, Applicants respectfully and properly defer addressing the present rejection until there is allowable subject matter in the present application. At that time, a terminal disclaimer will be filed if warranted by the Examiner's rejection in view of the allowed claims.

II. CLAIM REJECTIONS UNDER 35 U.S.C. § 112, ¶1, FOR FAILURE TO COMPLY WITH THE WRITTEN DESCRIPTION REQUIREMENT

The Examiner rejected Claims 1-10 and 20 under 35 U.S.C. § 112, ¶1, for failing to comply with the written description requirement. Office Action at 4-5. The Examiner stated:

> While claimed method is drawn to in vivo treating a patient by administering any cupredoxin comprising the mutant and truncated azurin and other species of cupredoxin. However, the specification only provides the teaching on treating a subject with wild type azurin, not other cupredoxin including elected species of plastocyanin and mutants or truncated azurin of SEQ ID NO: 6 and 7. As such, one skilled in the art

would not convince that the applicant had the possession of the claimed method of using any form of cupredoxin except of wild type of azurin.

Office Action at 4 (emphasis in original). Applicants respectfully traverse.

A. The Examiner's Rejection Focuses on a Limitation in Claim 5 and Does Not Separately Address Each Claim

The Examiner begins discussing the rejection by stating "[t]he claims are amended as drawn to a method of treating a condition related to resistance to cell death comprising administering cupredoxin, wherein the cupredoxin is an azurin comprising mutated or truncated azurin (claim 5)." Office Action at 4. The Examiner goes on to describe the purported insufficiencies of the specification's description of mutants and truncations of azurin. *See* Office Action at 4-5. Notably absent from the Examiner's discussion of the rejection of Claims 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 20 is any discussion of the limitations of Claims 1, 2, 3, 4, 6, 7, 8, 9 , 10 or 20. *See* Office Action at 4-5. It is a matter of basic patent law that patentability is determined on a claim-by-claim basis; the Examiner ignores this most basic of principles and rejects eleven claims based upon an analysis of a single element present in dependent claim 5. For this reason alone, Applicants respectfully request reconsideration and withdrawal of the Examiner's written description rejections of Claims 1, 2, 3, 4, 6, 7, 8, 9, 10 and 20.

B. The Examiner's Rejection Applies Improper Standards

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *See, e.g., Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1319 (Fed. Cir. 2003). An applicant complies with the written description requirement by describing the invention using "such descriptive means as words, structures, figures, diagrams, formulas, etc. that set forth the claimed invention." *Regents of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1666 (Fed. Cir. 1997). The written description requirement does not demand that the applicant have literal support in the specification for the claim language. *In re Kaslow*,

707 F.2d 1366, 1375 (Fed. Cir. 1983).

The Examiner's rejection misapplies or ignores these well-established standards. For example, the Examiner states that "description of in vitro assay of cytotoxicity to the cancer cells do not render applicant having a possession of in vivo treating a patient with cancer." Office Action, p. 6. However, this statement does not apply an appropriate written description standard. The specification does not need to teach in vivo administering for every compound claimed to satisfy the written description requirement. Instead, all that is required is to establish that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. *Kaslow*, 707 F.2d at 1375. It is an established principle that in vivo testing data is not required to show a compound has therapeutic utility: "If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process." MPEP § 2107.03; *see also id.* ("Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders, even with respect to situations where no art-recognized animal models existed for the human disease encompassed by the claims." (citations omitted)).[1] Thus, an applicant is not required to provide in vivo testing data.

Moreover, an applicant is not required to provide any working example in the specification. "A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language." *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1366 (Fed. Cir. 2006) (quoting *Lizardtech, Inc. v. Earth Resource Mapping, PTY, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005)). Only enough must be included to convince a person of

[1] Applicants' search of the Patent Office's issued patent database for patents containing "in vitro" and not "in vivo" yielded nearly 33,000 hits. Applicants search of the Patent Office's issued patent database for patents containing "in vitro" but not "in vivo" in the specification and having "method of treating a patient" in the claims, yielded 255 hits.

skill in the art that the inventor possessed the invention. *Id.* In sum, the Examiner is wrongly imposing an overly rigorous written description requirement that is not consistent with established principles. For this reason, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of Claims 1-10 and 20 for failure to comply with the written description requirement.

C. Applicant's Disclosure Is Sufficient to Convey That It Has Possession of the Claimed Invention

To the extent the Examiner's rejection is based upon an assertion that the compounds identified in the method claims are inadequately described, Applicants respectfully disagree. As a preliminary matter, the compounds recited in Claims 7 and 8 are specifically identified by sequence; Applicants' cannot contemplate a clearer description of a compound. In addition, and as Applicants stated previously, support for truncated and mutant cupredoxins is provided throughout the present application, e g., at paragraphs [014], [026], [027], [028], [078], [083-086], [0112-0120] and Examples 19-21 and Figures 11-13. *See also* U. S. Patent No. 7,089,105 (Ser. No. 10/047,710, filed January 15, 2002 from which the present application claims priority) which is coextensive with the present application and specifically discloses and claims truncated cupredoxins. As taught in paragraph [0112], mutations and/or truncations of cytotoxic factors can produce cytotoxic agents of varying compositions also demonstrating functional activity. Paragraphs [0112 -00120] teach how to develop a truncated or mutant cupredoxin from azurin or plastocyanin. Moreover, Examples 19-21 and Figures 11-13 teach that such cupredoxins do induce the apoptosis rate and cell cytotoxicity.

The Examiner argues that the "prophetic variants derivatives that applicant discussed . . . do not provide adequate support of the specific truncated for of azurin that would maintain the required function." Office Action at 5. However, the written description requirement for a claimed genus may be satisfied by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show

the applicant was in possession of the claimed genus. *See Amgen v. Hoechst Marion Roussel*, 314 F.3d 1313, 1332 (Fed. Cir. 2003); *Eli Lilly*, 119 F.3d at 1568.

In the present application, the specification teaches identifying characteristics, chemical similarities such as being electron transfer proteins and structural similarities of numerous cupredoxin compounds, including azurin and plastocyanin. *See, e.g.,* Paragraphs [070]-[075]. More importantly, the specification also identifies a key conserved structural characteristic. The specification shows azurin to be capable of binding to p53 protein via a hydrophobic patch, which patch forms part of the conserved structure shared by the cytotoxic cupredoxins of the invention. *See* Paragraphs [073]-[085]. The specification further describes the cytotoxic activity of azurin as "dependent upon the tumor cell having a functional p53 tumor suppressor gene." Paragraph [087]. In addition, it is reported that both azurin and plastocyanin share a G-H loop sequence which has high binding affinity for ephrinB2, and which exhibits a cytotoxic effect. *See* "Programmed Cell Death," 1995 Annual Report, Howard Hughes Medical Institute (Exhibit 1) and A. Chaudhari et al., Biochem. 46(7):1799-1810 (2007) (Exhibit 2). It is known in the art that one 18-amino acid truncation of burin in particular, Azu-113, has significant structural similarity to ephrinB2 at the "G-H loop" region and selectively binds the ephrinB2 receptor tyrosine kinase EphB2. Exhibit 2. The ability of this azurin truncation to induce cell death "can thus be ascribed to interference in EphB2 signaling." Id. It is also known in the art that plastocyanin has even greater structural similarity to ephrinB2 at the G-H loop sequence than azurin, and that it binds EphB2 with even greater affinity. Id. Further, data has shown that a variety of plastocyanin derived peptides comprising this G-H loop, structurally similar to the azurin G-H loop and ephrinB2, functions to arrest cell growth by inducing apoptosis. F. Lekmine et al., "The anticancer properties of plastocyanin derived peptides," American Association for Cancer Research Annual Meeting: Proceedings; 2007 April 14-18, Los Angeles, CA, Philadelphia, PA, Abstract No. 5607 (Exhibit 3). Thus, based on the written description and knowledge in the art as to the p53 binding of azurin, plastocyanin and truncations thereof, one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.

In addition, the specification teaches how to develop mutants, (Example 19), how to use these mutants for in vitro assays (Examples 20 and 21) and that a mutant can be used for treatment of cancer. Paragraph [0010]. Furthermore, the specification teaches in Examples 15, 16 and 18, how to administer cupredoxins to a patient in vivo. Because the specification teaches how to make the claimed cupredoxins and how to administer the cupredoxins of the present invention to a patient for treatment, one skilled in the art must reasonably conclude that the inventor had possession of the claimed invention.

For all the foregoing reasons, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of Claims 1-10 and 20 for failure to comply with the written description requirement.

III. CLAIM REJECTIONS UNDER 35 U.S.C. § 112, ¶1, FOR FAILURE TO COMPLY WITH THE ENABLEMENT REQUIREMENT

The Examiner rejected Claims 1-11 and 20 under 35 U.S.C. § 112, ¶1, for failing to comply with the enablement requirement. Office Action at 5-10. Specifically, the Examiner stated the pending claims are rejected because:

> the specification, while being enabling for a method of treating a condition related to resistance to cell death comprising administering to a patient a pharmaceutical composition of wild type azurin of SEQ ID NO:1 does not reasonably provide enablement for the method of administering any other cupredoxin comprising elected plastocyanin and mutated or truncated azurin comprising amino acid sequence of SEQ ID NO: 6 and7.

Office Action at 5-6. Applicants respectfully traverse.[2]

A. The Examiner's Rejection Fails to Separately Address Each Claim.

The Examiner's analysis focuses entirely on Claim 1. Notably absent from the Examiner's discussion of the rejection of Claims 2, 3, 4, 5, 6, 7, 8, 9, 10 and 20 is any

[2] The Examiner's enablement rejection is very similar to the Examiner's written description rejection; therefore, Applicants incorporate by reference their response to Examiner's written description rejection into their response to the Examiner's enablement rejection.

discussion of the individual elements of these claims. *See* Office Action at 4-5. Again, it is a matter of basic patent law that patentability is determined on a claim-by-claim basis; the Examiner ignores this most basic of principles and rejects eleven claims based upon an analysis of a single claim. For this reason alone, Applicants respectfully request reconsideration and withdrawal of the Examiner's enablement rejections of Claims 2, 3, 4, 5, 6, 7, 8, 9 , 10 or 20.

B. The Examiner Errs by Requiring In Vivo Data and Deeming In Vitro Data Insufficient.

The Examiner states:

> [The] claimed invention is drawn to in vivo treating a condition with mutated or truncated azurin or any cupredoxin, however, the specification shows neither the result of in vivo treatment with the cupredoxin (except wild type azurin), nor correlation between the in vitro cytotoxic activities and in vivo treatment in a patient. Thus, in the absence of this guideline, direction and experimentations, one skilled in the art would be unable to use claimed invention without an undue quantity of experimentations because the unpredictability of the nature of the invention.

Office Action at 6-7. The Examiner goes on to provide a lengthy, erudite analysis of the differences between in vivo and in vitro data. Office Action 8-10. As detailed as it might be, the Examiner's analysis analyzes each aspect of the comparison but one – the manner in which the law analyses the two types of data. *See id.* As Applicants explained in their response to the Examiner's written description rejection, the law simply does not require in vivo testing data to support claims to use of a compound to treat a patient. *See* MPEP § 2107.03. The Examiner's requirement is thus contrary to the law and improper. For this reason, Applicants respectfully request reconsideration and withdrawal of the Examiner's enablement rejections of Claims 1-10 and 20.

C. The Examiner Errs in Requiring that the Subject Compounds Have Identical Properties.

The Examiner states that "one skilled in the art has recognized that the mutated or truncated form of a toxin may not always have the same activities as its wild type form."

Office Action at 7. The Examiner goes on to discuss the Yamada reference and a particular mutant that "has very little toxicity compared to the wild type of azurin" because it is "deficient in forming a complex with p53." Office Action at 7. Based upon this, the Examiner concludes that "[b]ecause claimed invention for in vivo treatment a condition is unpredictable and because one skilled in the art has recognized the mutated azurins do not have the activities as wild type azurin undo experimentation would be necessary and required in order to use and practice claimed invention by one skilled in the art." Office Action at 7.

Here, the Examiner is seemingly requiring the relevant genus of compounds to have identical functionalities or, perhaps more specifically, identical levels of functionality. However, the Examiner is incorrect in imposing such a requirement. Per the claims, the compounds must "promote death in a cell demonstrating resistance to cell death." Claim 1. That some compounds in the group do this better than others does not mean the claims are not enabled. In that regard, claims may be enabled even if they are drawn to a genus of compounds that includes wholly inoperable embodiments. What is important is whether one of skill in the art could identify such embodiments without undue experimentation. *See Atlas Powder Co. v. E.I. Du Pont*, 750 F.2d 1569, 1576-77 (Fed. Cir. 1984); *see also In re Dinh-Nguyen*, 492 F.2d 856, 858-59 (CCPA 1974) ("It is not a function of the claims to specifically exclude possible inoperative substances."). For this reason, Applicants respectfully request reconsideration and withdrawal of the Examiner's enablement rejections of Claims 1-10 and 20.

D. The Subject Compounds Share a Common, Highly Conserved Structure Corresponding to their Functionality.

A specification that contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971).

The cytotoxic cupredoxins are described in the specification as sharing a common, highly conserved structure which includes, *inter alia*, a beta-barrel structure, a copper binding site consisting of a cluster of four residues, and a hydrophobic patch involved in binding interactions with various partners, including p53. See Paragraphs [073]-[085]. Additionally, as described above, it is known in the art that both azurin and plastocyanin share a G-H loop sequence which has great binding affinity for ephrinB2 and which exhibits a cytotoxic effect.

Thus, the present specification contains a teaching of the manner and process of making and using the intention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented, as required under *In re Marzocchi*. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections of Claims 1-10 and 20 under the enablement requirement of 35 U.S.C. § 112, ¶ 1.

E. The Exhibits Submitted Herewith are Proper Evidence of Enablement.

In this Reply, Applicants have provided definitive evidence in the form of specific references illustrating that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. *See* discussion above. Evidence provided by an applicant "need not be conclusive but merely convincing to one skilled in the art." MPEP § 2164.05. Applicants respectfully submit that the submitted references provide convincing evidence that "one skilled in the art would be able to make and use the claimed invention using the application as a guide." MPEP § 2164.05 (citing *In re Brandstadter*, 484 F.2d 1395, 1406-07, 179 USPQ 286, 294 (CCPA 1973)).

To overcome a prima facie case of lack of enablement, an applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. However, this does not preclude an applicant from providing a declaration after the filing date which demonstrates that the claimed invention works. *See* MPEP § 2164.05. It is clear that "[e]nablement of an anticipatory reference may be demonstrated by a later

reference." *Bristol Myers Squibb Co. v. Ben Venue Lab. Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001). Indeed, a party may properly rely on later publications to prove enablement of an earlier disclosure. *See, e.g.*, *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1335 (Fed. Cir. 2003) ("numerous post-filing publications demonstrated the extent of the enabling disclosure"); s*ee also In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) ("The [] declaration, though dated after applicants' filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification." (citing *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971))). Therefore, the fact that the references published after the filing date of the present application is irrelevant to their admissibility to show enablement of the present application.

Applicants respectfully submit that the Examiner should accept the submitted references as convincing evidence that the disclosure is enabling. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections of Claims 1-10 and 20 under 35 U.S.C. § 112, ¶ 1.

CONCLUSION

Applicants have properly stated and traversed each of the Examiner's grounds for rejection. Applicants note that the Examiner has withdrawn all rejections over the prior art and that the claims are therefore free of the prior art. Now that Applicants have addressed the Examiner's section 112 rejections, Applicants believe that the presented claims are in condition for allowance.

If the Examiner has any questions or believes further discussion will aid examination and advance prosecution of the application, a telephone call to the undersigned is invited. If there are any additional fees due in connection with the filing of this amendment, please charge the fees to undersigned's Deposit Account No. 50-1067. If any extensions or fees are not accounted for, such extension is requested and the associated fee should be charged to our deposit account.

Respectfully submitted,

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